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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KANTAMNENI, SHOBHA	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 02/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/643,699	DRUZGALA ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-29, 32 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-29, 32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/06/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation of 10/269,139, PAT 6,608,097. Claims 22-29, 32, and 33 are pending. Claims 22-29 and 32-33 are examined herein.

Election/Restrictions

Applicant's election of Group V claims 22-29, 32, and 33, drawn to a method of using various products in the reply filed on 08/09/2004 without traverse is acknowledged. Applicant further elects structure shown in Figure 3, as specie in the reply filed on 09/03/04. The restriction requirement is made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22, 32, and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for calcium channel blocking compounds of structures shown in Figures 1-9 of specification, does not reasonably provide enablement for blocking calcium channel by administering the **compounds in general having at least one of the characteristics of (a) to (h) in claim 22**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

The rejected claims are drawn to an invention, which pertains to a method for blocking a calcium channel in a patient, by the administration of a calcium channel blocking compound **having at least one of the characteristics (a) to (h) specified in claim 22.**

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a method of blocking a calcium channel by administering **a compound having any one of the characteristics from (a) to (h)**. The scope of the compounds claimed to be useful is extremely broad.

(3). Guidance of the Specification :

The guidance given by the specification as to what types of calcium channel blocking compounds have characteristics such as a short non-oxidative metabolic half-life, contain a hydrolysable bond that can be cleaved non-oxidatively, water soluble primary metabolites, or does not cause drug-drug interaction is limited. All of the guidance provided by the specification is directed to certain calcium channel blocking compounds. All of the guidance provided by the specification regarding calcium channel blocking compounds is directed to the following compounds: Verapamil, Diltiazem, Nifedipine, Mibefradil, Mibefradil analogs. Beyond these five different structural classes of calcium channel entry blockers, there is no guidance in the specification regarding what type of other compounds, would have characteristics as claimed from (a) to (h) of claim 22 in blocking calcium channel.

(4). Working Examples:

In the instant case, no working examples are presented in the specification as filed showing a method of blocking a calcium channel in a patient.

(5). State of the Art / Predictability of the Art:

The relative skill of those in the art is high.

The invention is directed to a method for blocking calcium channel by administering a calcium channel blocking compound having certain characteristics in general. It is well established that the **scope of enablement** varies inversely with the degree of unpredictability of the factors involved, and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839 (1970). It is further noted that the pharmaceutical art is unpredictable, requiring each embodiment

to be individually assessed for physiological activity. In the instant case, the claimed invention is highly unpredictable since one skilled in the art cannot fully describe the genus, visualize or recognize the identity of the claimed subject matter, except those particular agents disclosed in the specification by name. In the absence of fully recognizing the genus herein, one of skill in the art is unable to fully predict possible physiological activities of any compounds having claimed characteristic properties in the claimed method of treatment herein. Moreover, one of the skills in the art would recognize that it is highly unpredictable in regard to therapeutic effects of the compounds described in general, side effects such as adverse drug-drug interactions, serious toxicity that may be generated due to accumulation of drug itself or one of its metabolites that produce LFT elevations and carcinogenicity when and/or after administering to a host any calcium channel blocking compounds, especially Mibefradil analogs in the instant case. Because of the lack of ability to fully recognize the members of the genus herein, except those particular agents which are Mibefradil analogs disclosed in the specification, one of the skills in the art would not be able to fully predict the possible treatments herein and possible adverse effects occurring with many compounds having the claimed functional properties and their administration to a host in the claimed method herein. Thus, the instant claimed invention is highly unpredictable.

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of ordinary skill in the art would have to first envision a specific calcium channel blocking compound for the treatment, a dosage for each compound, the duration of treatment, route of treatment etc. One would

then need to test the compound in the model system to determine whether or not the compound is effective as a calcium channel blocker. One would then also need to test the compound in the model system for side effects and toxicity i.e magnitude of the change in the concentration of active species (parent drug and/ or active metabolite) at the site of pharmacological action and the therapeutic index of the drug. Thus a person of skill in the art would have to engage in undue experimentation to test all compounds encompassed in the instant claims and their combination with other drugs to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claims 22, 23-29, 32, and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **enablement requirement**. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The instant claims are drawn to the method for blocking calcium channel in a patient in need of such treatment comprising administering to said patient a specific type of compounds having the structures shown in claims 23-29 (**Mibefradil analogs**).

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

The rejected claims are drawn to an invention, which pertains to a **method for blocking a calcium channel in a patient**, by the administration of a calcium channel blocking compound having the structures shown in claims 23-29.

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a method of blocking a calcium channel by administering a compound having structures shown in claims 23-29. The breadth of the claims includes hundreds of compounds of structures shown in claim 23.

(3). Guidance of the Specification / (4). Working Examples: :

All of the guidance provided by the specification regarding calcium channel blocking compounds is directed to the following compounds: Verapamil, Diltiazem, Nifedipine, Mibefradil.

Specification as filed has **no working examples or tests** to show if the instant compounds referred to as soft calcium channel blockers do indeed possess calcium channel blocking ability.

(5). State of the Art / Predictability of the Art:

The relative skill of those in the art is high.

The invention is directed to a method for blocking calcium channel by administering a compound having structures shown in claims 23-29. Applicants have **not provided any evidence or disclosed tests** that are highly predictive for the pharmaceutical use for blocking calcium channel in a patient using the instant compounds. Pharmacological activity in general is highly unpredictable area. It is well established that the enablement varies inversely with the degree of unpredictability of the factors involved, and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839 (1970). For example, mibefradil demonstrated efficacy in the treatment of hypertension and angina pectoris in man, but was withdrawn by the manufacturer due to drug-drug interactions based on the inhibition of cytochrome P-450. In the instant case, the claimed invention is highly unpredictable because the enzymatic hydrolysis of the soft calcium channel blockers results in metabolites with acidic functional groups. These acidic metabolites will have higher solubility in water. Thus these novel mibefradil-based compounds and their

metabolites of the instant invention have different functional groups and result in different biological properties such as drug-drug interactions, formation of toxic metabolites or increased and longer exposure to the parent compound etc. Thus, the instant claimed invention is highly unpredictable and **Applicant did not provide any evidence or tests to show if these mibefradil-based compounds can be used as calcium channel blockers**.

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of ordinary skill in the art would have to first envision a specific soft calcium channel blocking compound of the instant invention for the treatment, a dosage for each compound, the duration of treatment, route of treatment etc. One would then need to test the compound in the model system to determine whether or not the compound is effective as a calcium channel blocker. One would then also need to test the compound in the model system for side effects and toxicity i.e magnitude of the change in the concentration of active species (parent drug and/ or active metabolite) at the site of pharmacological action and the therapeutic index of the drug. Thus a person of skill in the art would have to engage in **undue experimentation** to test these novel mibefradil-based compounds encompassed in the instant claims and their combination with other drugs to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent

protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In Claims 24-27, and 29 the compounds lack antecedent basis from claim 23. In claim 23 the R_{15} variable represents $-(CH_2)_nCOOR_{16}$, whereas in the claims 24-27, and 29 which depend on claim 23, R_{15} is hydrogen.

In Claims 24, and 26-29 the compounds lack antecedent basis from claim 23 because of the group attached to the 2-position of the 1,2,3,4-tetrahydronaphthalene ring. In claim 23 the group attached to the 2-position is $-X-C(=O)-OR_1$whereas in the compounds in claims 24, and 26-29 it is $-O-C(=O)-CH_2OR_1$.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22, 32, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Brance et al. (US 4,808, 605).

The instant invention is directed to a method for blocking calcium channel in a patient comprising administering the compounds in general having at least one of the characteristics of (a) to (h) in claim 22.

Branca et al. teach a method of treating or preventing ischemia, arrhythmia, and high blood pressure etc. comprising administering a calcium channel blocking compound of formula I having a hydrolysable bond as claimed in the instant invention. See column 3, lines 1-30; in formula I when R3 = lower-alkyl-carbonyl-oxy results in hydrolysable ester bond.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER